Erica Lueth
UROP Spring 2013
Dr. Venkatram Mereddy

Evaluation of MCT1 Inhibitors for Pancreatic Cancer

Pancreatic cancer is one of the most devastating cancer diagnoses a person can receive. An average of 40,000 Americans a year will be diagnosed with pancreatic cancer making it the fourth leading cause of death. After being diagnosed, the average survival is less than 5%. Once diagnosed, patients have to endure a miserable set of chemotherapy treatments that leave them weak and fragile.

During my Fall 2013 UROP, I wanted to test some derivatives based on nobel cyanohydroxycinnamate (CHC)-based monocarboxylate transporter 1 (MCT1) inhibiters as potential anticancer agents[1]. Their lab had sythnesized and evaluated more than 250 new compounds. From these studies, several potent MCT1 inhibitors that are highly active were discovered. The goal however was not only to find an anticancer agent, but also to have the molecule be completely nontoxic so the patient can have a better quality of life while undergoing treatment.

Using nude mice affected with colon cancer they were able to confirm that the compounds had reduced the tumor and not caused toxicity. Further testing was then done to see what affect the molecules had on pancreatic cancer. MCT1 has been identified in a large number of invasive pancreatic cancers. Using three different cell lines *in vitro*, we were able to test the efficiency of the compounds.

Inhibitors of MCT1 transporters may alter cell viability depending on their specificity, affinity, and intracellular access[2]. Therefore, the synthesized compounds that exhibited the highest MCT1 inhibition were evaluated for their cytotoxicity in pancreatic cell lines. We utilized MIA PaCa-2 (Pancreatic Adenocarcinoma) for the study. A standard commercially available SRB viability assay that measures cellular protein for the *in vitro* cytotoxicity assays were used.

The cells used for the study were cultured to confluence in 48-well plates by standard methods. Test compounds were added to each well and incubated for 72 hours. Controls included non-treated wells, gemcitabine, and combinations of the test compounds. Each assay was measured in triplicate and the mean value was calculated. Compounds that exhibited the highest toxicity (IC_{50} < 10 μM) were identified as lead molecules for further studies.

After the test some molecules showed very good toxicity and some molecules did not show confirmable results. Testing was done a few times using different cell lines for accuracy. The molecules that showed good toxicity were isolated for the next trials of testing while the molecules with poor results were examined and different structures were discussed.

I hope to continue my research in the future and move onto the next level of testing including small animals to check for toxicity and then actual *in vivo* cancer studies using a tumor implanted in the animal to check how well the compound attacks the cancer. I hope that one day this compound will be able to complete all rounds of testing and possibly someday be used as a drug sold in local pharmacies.

Further testing will be needed and that will take time and effort but I believe if I work hard I will be able to prove the toxicity of my compound to cancer.